

# Use of commercial anti-penicillin IgE fluorometric enzyme immunoassays to diagnose penicillin allergy

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**Background:** The intermittent unavailability of penicilloyl-polylysine since September 2000 has focused interest on commercial anti-penicillin IgE fluorometric enzyme immunoassay (FEIA) tests to evaluate penicillin allergy. There has been no published comparison of commercial anti-penicillin IgE FEIAs and penicillin skin testing performed in the United States.

**Objective:** To determine whether the current commercial anti-penicillin IgE FEIAs can replace or augment penicillin skin testing and oral challenges when evaluating individuals with a history of penicillin allergy for future therapeutic penicillin tolerance.

**Methods:** A prospective convenience sample of 150 individuals with a history of penicillin allergy were evaluated between January 23, 2007, and August 4, 2009, with both penicillin skin tests and commercial anti-penicillin IgE FEIAs to penicillin G, penicillin V, and amoxicillin. All individuals with a negative penicillin skin test result underwent oral penicillin class antibiotic challenges. All individuals with a positive anti-penicillin IgE FEIA result also underwent oral penicillin class antibiotic challenges.

**Results:** Six individuals (4.0%; 95% confidence interval [CI], 0.9% to 7.1%) had positive penicillin skin test results, and none had positive FEIA results. Four individuals (2.7%; 95% CI, 0.1% to 5.3%) had positive FEIA results, and none had positive penicillin skin test results. Three individuals (2.0%; 95% CI, -0.2% to 4.2%) had positive oral challenge results, 1 with hives at 6 hours after challenge and 2 with delayed-onset (at >24 hours) nonurticarial rashes, and none had positive FEIA results.

**Conclusions:** The current commercial anti-penicillin IgE FEIAs are not useful in diagnosing penicillin allergy in patients with remote histories of penicillin allergy. Penicillin skin testing and, if the results are negative, an oral challenge remain the criterion standard tests to determine therapeutic penicillin tolerance.

*Ann Allergy Asthma Immunol.* 2010;105:136–141.

## INTRODUCTION

Skin testing for penicillin allergy has been limited during the past decade because of the lack of commercially available penicillin skin test (PST) reagents. The major determinant penicilloyl-polylysine (Pre-Pen) was off the market from September 2000 to November 2001 and from September 2004 to November 2009. Because of this, there has been a renewed interest in the use of commercial anti-penicillin IgE fluorometric enzyme immunoassay (FEIA) tests to detect penicillin allergy. Our hypothesis was that commercial anti-penicillin IgE FEIAs could not replace PSTs.

In vitro tests for the detection of IgE antibodies against penicillin have been studied since the 1970s.<sup>1</sup> Phadia, Upp-

sala, Sweden, is the maker of the only commercial anti-penicillin IgE FEIAs for sale in the United States. Their original Phadebas radioallergosorbent test (RAST) was launched in 1974. Their updated capacity (CAP) FEIA system was launched in 1989. It is currently marketed in the United States under the trade name ImmunoCAP and in Europe as the CAP system FEIA. The US Food and Drug Administration allows the sales of these commercial anti-penicillin IgE FEIAs for diagnostic purposes by prescription use. They are grandfathered in as substantially equivalent to tests that existed before May 28, 1976.

There have been no published studies performed in the United States that have studied individuals with a history of penicillin allergy with PSTs; commercial anti-penicillin IgE FEIAs directed against penicillin G, penicillin V, and amoxicillin; and oral challenges in all PST-negative individuals. Several European groups have evaluated individuals with a history of penicillin allergy with PSTs and commercial anti-penicillin IgE FEIAs or RASTs.<sup>2–8</sup>

## METHODS

This study was approved by the Kaiser Permanente Southern California Institutional Review Board. All participants provided written informed consent for penicillin allergy testing and oral challenges. This article complies with the European

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**Disclosures:** Authors have nothing to disclose.

Received for publication March 29, 2010; Received in revised form June 17, 2010; Accepted for publication June 19, 2010.

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doi:10.1016/j.anai.2010.06.014

Academy of Allergy and Clinical Immunology position paper on nomenclature for allergy.<sup>9</sup>

Study participants were a prospectively collected convenience sample of patients tested by the Kaiser Permanente San Diego Allergy Department between January 23, 2007, and August 4, 2009. The sample minimized selection bias by consecutively selecting every accessible person who met the entry criteria and consented to the study. This study includes 18 individuals tested between January 23, 2007, and January 4, 2008, who have been partially described previously.<sup>10</sup> Individuals with a history of toxic epidermal necrolysis, Stevens-Johnson syndrome, hemolytic anemia, hepatitis, nephritis, or oral and/or skin blisters associated with or attributed to the previous use of a penicillin class antibiotic were not offered penicillin skin testing. All patients had a history of penicillin allergy based on symptoms attributed to penicillin use. These symptoms included anaphylaxis, respiratory problems, hives, other poorly characterized rashes, local swelling at the site of injection, gastrointestinal symptoms, unknown symptoms, or other symptoms not specifically excluded. All electronic medical records were reviewed by a single investigator (E.M.). Posttesting antibiotic use, adverse reaction, and drug allergy data were obtained through November 30, 2009.

Penicillin skin testing was performed as previously described in detail.<sup>11</sup> Positive test results were defined as a 5-mm or larger wheal with flare greater than wheal.<sup>11</sup> All patients were tested with the major determinant penicilloyl-polylysine ( $6 \times 10^{-5}$ M); the minor determinants penicillin (0.01M, 3.56 mg/mL), penicilloate (0.01M, 3.75 mg/mL), and penilloate (0.01M, 3.32 mg/mL); and amoxicillin (0.01M, 3.65 mg/mL). Penicilloyl-polylysine was produced in the Kaiser Permanente Southern California Regional Immunology Laboratory, as previously reported.<sup>10</sup> Penicilloate and penilloate were produced as previously reported.<sup>11</sup> An oral amoxicillin, 250 mg, or oral penicillin, 500 mg, challenge was given to all PST-negative individuals. Oral penicillin was given to the rare individual who had active syphilis and would require immediate parenteral penicillin therapy, if the penicillin skin test and oral challenge results were negative. Patients were observed for 1 hour after the oral challenges. Patients who were taking parenteral penicillin for syphilis were observed for an additional hour.

Anti-penicillin IgE FEIAs (Phadia ImmunoCAP) for penicilloyl G (c1), penicilloyl V (c2), and amoxicillin (c6) were performed according to the manufacturer's specifications. Positive test results were defined by the manufacturer as greater than 0.11 kUA/L or class I or greater. The Kaiser Permanente Southern California Immunology laboratory that performed the FEIAs performed 400,483 total ImmunoCAP tests of all kinds during 2008.

Sample size for this study was determined by assuming that 1 or more FEIA results would be positive approximately 20% of the time in PST-positive individuals. This assumption was partially based on preliminary work performed before this study. We had 1 anecdotal report of a positive commer-

cial anti-penicillin IgE FEIA seen in our health plan in a penicillin skin test-positive individual in the early 2000s. Because our health care records were not completely electronic at that time, we were unable to confirm the report. This anecdote, coupled with the approximately 32% concordance seen in the 1996 paper by Sanz et al,<sup>4</sup> led us to assume that 20% would be a reasonably expected concordance. For commercial anti-penicillin IgE FEIAs to replace PSTs, at least 1 FEIA result would have to be positive 90% of the time when the PST result was positive. It was assumed that only 5% of PSTs would be positive based on recent work by us.<sup>10</sup> This resulted in a sample size of 180 to have an 80% chance of seeing this difference if it existed. The data were analyzed for 150 patients because there were no positive FEIA results in PST-positive individuals. It is unlikely that obtaining 30 additional patients would have changed the conclusions. Even if 1 or 2 more PST-positive individuals were identified and they also had positive commercial anti-penicillin IgE FEIA results, there still would be an insufficient concordance.

Hypothesis testing for continuous variables was by means of the *t* test and for categorical variables by the  $\chi^2$  test. Nominal statistical significance was set at *P* = .05 (2-sided). All statistical analyses were performed using SAS Enterprise Guide Version 4 statistical software (SAS Institute Inc, Cary, North Carolina).

## RESULTS

Patient demographics are presented in Table 1. Women predominated and patients tended to be late middle-aged. The mean time since index reaction was almost 3 decades. Patients closely matched the population distribution of individuals with a history of penicillin allergy.<sup>10,12</sup>

Testing results and challenge reactions are presented in Table 2. Six patients (4.0%; 95% confidence interval [CI], 0.9% to 7.1%) were PST positive. Four patients (2.7%; 95% CI, 0.1% to 5.3%) were FEIA positive. All were positive to penicillin G. One patient was also positive to penicillin V, and 1 was also positive to amoxicillin. There were no PST-

Table 1. Study Participant Demographics

Demographics	No. (%) of patients <sup>a</sup> (N = 150)
Female	104 (69.4)
Age, mean (SD), y	51.8 (18.8)
Race	
White	92 (61.3)
Hispanic	27 (18.0)
Black	6 (4.0)
Asian	6 (4.0%)
Unknown, multiple, or other	19 (12.7)
Time since reaction, mean (SD), y	28.0 (18.8) <sup>b</sup>
Posttest follow-up, mean (SD), mo	12.7 (6.8)

<sup>a</sup> Data are presented as number (percentage) of patients unless otherwise indicated.

<sup>b</sup> N = 133.

Table 2. Testing and Challenge Results

Result	No. (%) of patients
PST positive	6 (4.0) <sup>a</sup>
FEIA positive	4 (2.7) <sup>b</sup>
Oral challenge positive	3 (2.0) <sup>c</sup>
PST and FEIA positive	0
FEIA positive and oral challenge positive	0
PST positive and oral challenge positive	Not done

Abbreviations: FEIA, fluorometric enzyme immunoassay; PST, penicillin skin test.

<sup>a</sup> One positive to each of the following: puncture to penicilloyl; intradermal to penicillin and amoxicillin; intradermal to penilloate, penicilloate, amoxicillin, and penicilloyl; intradermal to penicillin; intradermal to amoxicillin and penicilloate; and intradermal to penilloate and penicilloate.

<sup>b</sup> All were positive to penicillin G (0.25, 2.34, 0.66, and 4.89 kUA/L), 1 was also positive to penicillin V (6.58 kUA/L), and 1 was also positive to amoxicillin (0.26 kUA/L).

<sup>c</sup> One had hives at 6 hours, and 2 had delayed-onset nonurticarial rashes starting at greater than 24 hours.

associated adverse reactions. Three patients (2.0%; 95% CI, -0.2% to 4.2%) had challenge reactions, 1 with hives at 6 hours and 2 with delayed-onset (at >24 hours) nonurticarial, macular papular, rashes. None of the PST-positive patients were FEIA positive. None of the FEIA-positive patients were PST positive. None of the patients with challenge reactions were FEIA positive.

Eight patients (5.3%; 95% CI, 2.7% to 8.9%) reported acute transient subjective itching within 1 hour after oral challenge. None had persistent or delayed reactions and none had visible hives or any other rashes. These 8, and 1 additional patient who noted transient nausea, did not require any therapy and all were female. All 8 individuals with transient subjective itching had a clinical history of a chronic itching syndrome, such as chronic urticaria, eczema, or itching from hepatitis. Two individuals (25%) had subjective challenge reactions who then received therapeutic penicillins. One had 3 courses of penicillin and the other had 2 courses of amoxicillin, with no further reactions noted. None of the individuals with subjective reactions were FEIA positive.

Table 3 gives the number of patients exposed to penicillin and nonpenicillin antibiotics. Adverse reactions noted during the mean (SD) 12.7 (6.8)-month follow-up are reported. Thirty-six PST-negative patients (25%) were exposed to a total of 60 courses of penicillins, with 2 (3.3%) delayed-onset reactions noted. One was a macular papular rash that started 21 days after the patient started taking amoxicillin. The reaction was attributed by the patient's primary care physician to the amoxicillin. The other was a rash that started 4 days into a course of dicloxacillin. The patient had previously tolerated dicloxacillin 4 months earlier, immediately after testing. Two of the 4 FEIA-positive patients received penicillins and neither had a reaction. One was a 73-year-old man given dicloxacillin for cellulitis, and 1 was a 55-year-old

woman given amoxicillin for an upper respiratory tract infection. Seventy-seven patients (51.3%) were exposed to a total of 253 courses of nonpenicillin antibiotics. Of these, 27 (35.1%) had both a penicillin and a nonpenicillin antibiotic. Nonpenicillin antibiotic-associated reactions occurred in 6 individuals (2.4% per exposure). No significant difference was seen in the adverse reaction rate per course between penicillin (2/60; 3.3%) and nonpenicillin (6/253; 2.4%) antibiotics ( $P = .65$ ).

Patients averaged a mean (SD) of 1.25 (1.67) drug allergies at the end of the follow-up period, and most of these allergies were to antibiotics (0.96 [1.30]). Ten individuals (6.7%) had penicillin allergy noted in their records at the end of the follow-up period. Fifty-one (34.0%) were allergic to sulfonamide, 20 (13.3%) to cephalosporin, 14 (9.3%) to macrolide, 11 (7.3%) to quinolone, 10 (6.7%) to tetracycline, and 28 (18.7%) to other antibiotic allergies noted.

Five patients (3.3%) had a diagnosis of syphilis. All had negative PST, FEIA, and challenge results. All received intramuscular penicillin G, and none had any therapy-associated reactions.

Because this study used a sample of convenience, we also collected outcomes data on all of the 307 other individuals who had PSTs and oral challenges, if the results were negative, at our medical center but not commercial anti-penicillin IgE FEIAs during the study period. We have partially reported on 148 of these individuals previously.<sup>10</sup> This PST-only group was younger than study subjects, with a mean (SD) age of 43.2 (24.4) years ( $P < .001$ ). They were also predominately female (62.5%). There were only 3 PST-positive individuals (1.0%), significantly fewer compared with the study subjects ( $P = .03$ ). There were only 2 challenge reactions (0.7%), 1 with hives starting within 30 minutes of the challenge and 1 delayed-onset rash starting at approximately 24 hours. No difference was seen in the rate of oral challenge reactions in the PST-only group compared with the study patients (2/304 vs 3/144,  $P = .18$ ). Five PST-negative individuals (1.6%), again all females, had acute subjective

Table 3. Therapeutic Antibiotic Use After Testing and Adverse Reactions Noted

Therapeutic antibiotic courses	No. of patients exposed (total No. of courses)	No. of reactions (% per course)
Penicillins	36 (60)	2 (3.3) <sup>a,b</sup>
Nonpenicillin antibiotics <sup>c</sup>	77 (253)	6 (2.4) <sup>a,d</sup>

<sup>a</sup>  $P = .65$ .

<sup>b</sup> Neither were anti-penicillin IgE fluorometric enzyme immunoassay positive.

<sup>c</sup> Including cephalosporins, sulfonamides, macrolides, tetracyclines, quinolones, and other nonpenicillin antibiotics.

<sup>d</sup> No reactions were seen in 27 individuals exposed to 42 courses of cephalosporins. Two reactions were noted in 17 individuals receiving 25 courses of sulfonamides.

itching, without rash, within 1 hour of the challenge. This rate was lower than among the study patients (5/304 vs 8/144,  $P = .02$ ).

Ninety-three PST-only patients (30.3%) received a total of 137 courses of penicillins during their 18.8 (10.1)–month follow-up. Five reactions (3.6% per exposure) were attributed to the penicillin use in 5 individuals. A total of 172 PST-only patients (56.0%) were exposed to a total of 684 courses of nonpenicillin antibiotics. Of these, 71 (41.2%) had both a penicillin and a nonpenicillin antibiotic during the follow-up period. Twenty-three nonpenicillin antibiotic reactions (3.4% per exposure) occurred in 18 individuals. Again, no difference was noted in the adverse reaction rate between penicillin and nonpenicillin antibiotics ( $P = .80$ ).

On the basis of the information provided by Phadia, approximately 70 institutions were using the ImmunoCAP FEIA for penicillin allergy diagnosis in the United States during 2008. In addition, approximately 12,400 penicillin G (c1), 9700 penicillin V (c2), and 6000 amoxicillin (c6) tests were sold during 2008 in the United States.

## DISCUSSION

We noted no concordance between commercial anti-penicillin IgE FEIA results and PST or oral challenge results in our study cohort. Previous studies that performed both penicillin skin testing and commercial anti-penicillin IgE FEIAs or RASTs on individuals with a history of penicillin allergy are compared with the current report in Table 4.<sup>2-4,11</sup> Additional studies have looked at selected populations in which all participants were PST positive<sup>5,6</sup> or all were PST negative<sup>5,8</sup> and thus not directly comparable. The rate of positive PST results has decreased steadily since the 1970s. The concordance between positive PST and FEIA or RAST results has also decreased. The data do not support use of commercial anti-penicillin IgE FEIAs in lieu of PSTs and oral challenges for diagnosing clinically significant penicillin allergy. Overall, there is no compelling evidence that commercial anti-penicillin IgE FEIAs reliably identify individuals with remote histories of penicillin allergy who are at risk of clinically significant reactions with future therapeutic courses of peni-

cillins and who would not be identified using PSTs and oral challenges.

We would not consider the patient demographics of the current report to be a limitation. This study was meant to give real-world data that apply to the average patient in the United States who has a history of penicillin allergy. There may be higher rates of positive penicillin skin test results and even positive commercially available anti-penicillin IgE FEIA results in individuals with more recent reactions or with strong histories of anaphylaxis, but most individuals with a history of penicillin allergy have not had recent reactions or anaphylaxis.

A potential weakness of our current report is still the relatively small number of commercially available anti-penicillin IgE FEIA-positive individuals in our cohort given oral challenges and then followed up in the long term for reactions occurring with future therapeutic penicillin use. The 4 negative oral challenge results in PST-negative but FEIA-positive individuals reported herein provide some evidence of the lack of clinical utility for the current commercially available anti-penicillin IgE FEIAs. In the study by Silva et al,<sup>8</sup> an oral challenge only after the negative PST result would have safely identified the 2 FEIA-positive and oral challenge-positive individuals. The FEIAs did not preclude the need for oral challenges in the other PST-negative individuals. Only 9 individuals were PST positive of the 457 total tested (2.0%) at our medical center during the study period, and 6 (66.7%) were in our study.

We have previously shown that PSTs using some or all of our self-produced noncommercial materials are safe and effective.<sup>10,11,13-18</sup> We again document the continued decreasing rate of positive PST results, consistent with our previous report.<sup>10</sup> We again note seeing PST-associated reactions less frequently than groups that use higher reagent concentrations.<sup>19</sup> We again provide further documentation that using a 5-mm or greater wheal as the definition of a positive PST result reduces the number of false-positive test results in women with a remote history of penicillin allergy, compared with using 3 mm or greater.<sup>10,20</sup> This is supported by the low rate of positive challenge reactions and the low rates of future

Table 4. Published Comparisons Among Penicillin Skin Test, Commercial Anti-penicillin IgE FEIAs or RASTs, and Oral Challenge Results

Source	Patients with history of penicillin allergy, No.	PST-positive patients, No. (%)	RAST- or FEIA-positive patients, No. (%)	RAST- or FEIA-positive patients if PST positive, No. (%)	PST-negative and oral challenge-positive patients, No. (%)
Current report, 2010	150	6 (4.0)	4 (2.7)	0	3 (2.1)
Silva et al, <sup>7</sup> 2009	54	6 (11.1)	8 (14.8)	1 (16.6)	2 (4.9) <sup>a</sup>
Sanz et al, <sup>4</sup> 1996	149	44 (29.5)	26 (17.4)	14 (31.8)	Not done
Jarish et al, <sup>3</sup> 1981	51	17 (33.3)	12 (23.5)	11 (64.7)	Not done
Basomba et al, <sup>2</sup> 1979	81	63 (77.8)	37 (45.7)	36 (57.1)	Not done
Total	485	136 (28.0)	87 (17.9)	62 (45.6)	

Abbreviations: FEIA, fluorometric enzyme immunoassay; PST, penicillin skin test; RAST, radioallergosorbent test.

<sup>a</sup> Oral challenges were only given to the 41 patients who were both PST negative and FEIA negative.



adverse reactions with therapeutic courses of penicillins noted in this report.

Delayed-onset reactions, mediated by non-IgE mechanisms such as T-cell sensitization, are not predicted by PSTs. Hives occurring 1 to 6 hours after an oral challenge, as we noted in 1 study participant and in 1 PST-only individual, can be IgE-mediated events. Both types of reactions can be clinically significant and are good reasons to continue to perform oral challenges after negative PST results. Although we agree with Bousquet and coworkers<sup>21</sup> as to the utility of oral challenges after negative PST results, we report lower positive oral challenges rates. Acute transient itching without rash is a common occurrence after oral challenge in PST-negative individuals, particularly in women with a history of chronic itching, and does not appear to have any clinical significance.

Approximately 1.5% of women and 1.1% of men will report a new "penicillin allergy" after penicillin use.<sup>12</sup> During the time this study covers, only 14 of 457 individuals (3.1%) with a history of penicillin allergy tested in our medical center have had positive PST or oral challenge results. Patients with a history of penicillin allergy, even if PST and oral challenge negative, will still have an adverse reaction rate of approximately 3% per course of therapeutic antibiotic used, independent of antibiotic class, which is higher than the rate noted in random patients.<sup>10</sup>

The anti-penicillin IgE immunochemistry literature is difficult to evaluate because the serum donors with a history of penicillin allergy often have unreported PST and oral challenge statuses. In a large study by Zhao and coworkers<sup>22</sup> in 2002, looking at 1,797 individuals with a history of penicillin allergy, only 138 (7.7%) had IgE directed against benzylpenicillin using a noncommercial assay. The clinical significance of these IgE antibodies is questionable because 123 (89.1%) also had detectable anticephalothin IgE. The rate of significant clinical cross-reactions between penicillins and cephalosporins is at least an order of magnitude lower.<sup>23,24</sup> Future work will have to concentrate on PST-positive or challenge-positive individuals to develop useful commercial anti-penicillin IgE FEIAs or other in vitro tests.

In summary, the current commercial anti-penicillin IgE FEIAs are of no apparent use in evaluating individuals with a history of penicillin allergy. The FEIA results are positive too infrequently in PST-positive individuals to replace PSTs. There is no evidence that these current FEIAs identify individuals who would have serious IgE-mediated reactions with penicillin use that would not be identified using PSTs and oral challenges. It is essential that commercially available penicilloyl-polylysine remain on the market. Ideally, appropriate concentrations of prepackaged penicillin and amoxicillin should be marketed with the penicilloyl-polylysine to improve ease of use. It would also be advantageous to have the minor determinants, penilloate and penicilloate, made commercially available. In the current study, 1 PST-positive individual would have been missed without penilloate and penicilloate. Penicillin skin testing using a complete panel of reagents at appropriate concentrations and with appropriate

positive test result criteria, followed by oral challenges in PST-negative individuals, remains the criterion standard test to safely determine clinically significant IgE-mediated penicillin allergy.

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